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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/815,925	04/02/2004	Klaus Bosslet	DEAV1993/B005 US CNT 2	9424

5487 7590 03/06/2007

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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	**PAPER NUMBER**
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	03/06/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 03/06/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/815,925	BOSSLET ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *8 and 19-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 9-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

The Election filed on December 14, 2006 in response to the Restriction Requirement of November 29, 2006 has been entered. Applicant's election, with traverse, of Group I, Claims 1-7 and 9-18, as specifically drawn to a compound comprising a bifunctional fusion glycoprotein or bifunctional glycoprotein conjugate, the compound comprising a carbohydrate complement, and: a) a fist portion which is an enzyme; b) a second portion which binds specifically to an epitope of a tumor specific antigen; wherein the carbohydrate complement comprises at least one exposed terminal carbohydrate residue is acknowledged. The traversal is on the grounds that Groups I and Group II claim the same invention because the key concept is that the protein which possesses enzymatic activity can be an enzyme or a catalytic antibody. In another twist, Applicants assert that if a catalytic antibody is the protein with enzymatic activity and catalytic ability, it can be categorized as a catalytic antibody. Applicants further assert that the inventions of Groups I and II do not impose a serious search burden on the Examiner because when "enzyme" is searched, it is bound to reveal information concerning protein catalyst including catalytic antibodies with catalytic activity. Moreover, Applicants contend that the since the Groups I-II claim products and Groups III-IV are related to processes of making and methods of using such products, a search for the claimed products of Groups I-II is bound to reveal information concerning their process of making and their methods of use. Therefore, Applicants assert that performing the search covering the products; their process of making and method of use would not be a serious burden on the Examiner.

These arguments have been carefully considered, but have not been found persuasive.

Regarding the inventions of Groups I and II, the Examiner acknowledges and agrees that both the enzyme and catalytic antibody have enzymatic activity; and therefore, have a similar function. However, the Examiner recognizes that the specifically claimed "enzymes", see claim 7 drawn to specific species of enzymes, have no substantial structural similarities. In other words, the enzymes recited in claims 7 are single chain amino acid molecules, whereas the catalytic antibodies recited in Group II encompass antibodies including IgG which comprises 2 heavy and 2 light chains

containing constant and variable regions, and include framework regions which act as a scaffold for the 6 complementarily determining regions (CDR) that function to bind an epitope. As to the question of burden of search, the inventions are classified differently, necessitating different searches of the US Patents. Further, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not coextensive and is much more important in evaluating the burden of search. Different searches and issues are involved in the examination of each group.

For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Claims 1-21 are currently pending.
Claims 8 and 19-21 are withdrawn from consideration as being drawn to non-elected inventions.
Claims 1-7 and 9-18 are currently under consideration.

Species Election

The election of the following species is acknowledged:

- -β-glucuronidase for claim 7; and
- -anti-CEA for Claim 9.

Priority

Applicant is reminded that in order for a patent issuing on the instant application to obtain the benefit of priority based on priority papers filed in parent Application No.'s 09/302,434, 8/663,406 and 08/235,395 under 35 U.S.C. 119(a)-(d) or (f), a claim for such foreign priority must be timely made in this application. To satisfy the requirement of 37 CFR 1.55(a)(2) for a certified copy of the foreign application, applicant may simply identify the application containing the certified copy.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is apparent that the recited antibody is required to practice the claimed invention, because they are specifically required in the claims. As required elements they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification, or otherwise readily available to the public. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of the cell lines listed in claim 7. See 37 CFR 1.802.

The specification does not provide a repeatable method for obtaining the antibody and they do not appear to be readily available material. Deposit of the antibody would satisfy the enablement requirements of 35 U.S.C. 112. While the specification provides enough information for one of skill in the art to produce a monoclonal antibody with properties similar to those of the BW431/26 monoclonal antibody, the claims read a conjugate where a monoclonal antibody identical to the monoclonal antibody BW431/26 is required. However, reproduction of an identical monoclonal antibody is an unpredictable even.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of this application, access to the invention will be afforded to one determined by the Commissioner to be entitled thereto;
(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon granting of the patent;
(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;
(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and
(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803 - 37 CFR 1.809 for additional explanation of these requirements.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-7, 9-13 and 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seemann (Canadian Patent Application 2,062,047; laid open to the public on 8/29/1992) in view of Mattes (U.S. Patent 4,859,449; issued 08/1989) or Winkelhake (Winkelhake, J. Biological Chemistry, 251(4): 1074-1080, 1976).

Seemann teaches a fusion protein comprising the general formula huTuMAb-L-β-gluc, wherein huTuMA is a humanized tumor-specific moloclonal antibody or fragment thereof , L is a linker and β-gluc comprises human β-glucuronidase (page 1, 1st paragraph). With regards to huTuMAb, Seemann et al. teach that the huTuMAb includes the antibody binding fragments of anti-CEA BW431/26 monoclonal antibody (page 3, lines 16-23; page 17, lines 25+; and page 23, *Example O*). Moreover, Seemann et al. teach the fusion proteins can be further modified in order to achieve an increased half-life, wherein the fusion proteins are treated with an oxidizing agent which cleaves the carbohydrate ring, e.g. chemical degradation, which can be further derivatized by reductive animation which generates a new carbohydrate residue (page 4, lines 12-30). Seeman et al. further teach a pharmaceutical composition comprising the fusion protein, wherein the fusion protein was dissolved in tris/HCl buffer (*page 25, Example Q*).

Seemann does not explicitly teach that the fusion proteins or conjugates comprise an exposed galactose, mannose, N-acetylglucosamine, lactose, N-acetyllactose, glucose or fucose.

Mattes teaches chemical methods for addition of galactose or glucose to an anti-CEA antibody for increased clearance (col. 7, lines 6-col. 8, line 8). Mattes further teaches enzymatic methods of carbohydrate degradation (col. 6, lines 47-64). Moreover, Mattes teaches the desirability of increased clearance of therapeutic antibodies from the blood for the purpose of reducing side effects of antibodies or antibody conjugates caused by the presence of the antibody or antibody conjugate in the circulation.

Winkelhake teaches methods of enzymatic degradation (page 1075, 2nd col.).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the references so as to modify the fusion protein taught by Seemann with a galactose or mannose in view of the teachings of Mattes and Winkelhake because both Mattes and Winkelhake teach the increased clearance of modified antibodies is via the Ashwell receptors (asialoglycoprotein receptors) in the liver that recognize sugars such as galactose or mannose. Thus, it is well known in the art to modify antibodies by either adding a sugar such as

galactose by chemical means or by enzymatically degrading sialated carbohydrate groups using enzymes such as neuraminidase to expose sugars such as galactose. As such, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the fusion protein taught by Seemann with a galactose or mannose in view of the teachings of Mattes and Winkelhake , one would achieve a fusion protein having increased clearance from the circulation.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Seemann (Canadian Patent Application 2,062,047; laid open to the public on 8/29/1992) in view of Winkelhake (Winkelhake, J. Biological Chemistry, 251(4): 1074-1080, 1976) and in further view of Page (U.S. Patent 5,545,405; issued 08/1996; filed 10/1991).

Seemann in view of Winkelhake teach, as applied to claims 1-7, 9-13 and 15-16 above, a recombinantly made fusion glycoprotein comprising the antigen binding fragment of the monoclonal antibody BW431/26 made in BHK cells linked to a β-glururonidase having an exposed galactose residue.

Seemann in view of Winkelhake do not explicitly teach that the fusion protein is made in CHO cells.

Page teaches a method of producing antibodies and antibodies having CHO glycosylation using Chinese hamster ovary (CHO) cell lines (column 1, lines 11-14).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the references so as to produce the fusion protein taught by Seemann in view of Winkelhake using CHO cells in view of Page. One would have been motivated to do so because Page teaches that the use of CHO cells to make antibodies is known in the art (see for example, Col. 2, line 51 to Col. 6, line 26). Thus, one of ordinary skill in the art would have a reasonable expectation of success that by using CHO cells in view of Page, one would achieve a method of producing a fusion protein.

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Seemann (Canadian Patent Application 2,062,047; laid open to the public on 8/29/1992) in view of Mattes (U.S. Patent 4,859,449; issued 08/1989) or Winkelhake (Winkelhake, J. Biological Chemistry, 251(4): 1074-1080,

1976) and further in view of Bosslet (Bosslet et al, Br. J. Cancer 65: 234-238, 1992) and Jahde (Jahde et al, Cancer Res. 52: 6209, 1992;).

Seemann in view of Mattes or Winkelhake teach, as applied to claims 1-7, 9-13 and 15-16 above, a pharmaceutical composition comprising a recombinantly made fusion glycoprotein comprising the antigen binding fragment of the monoclonal antibody BW431/26 linked to a β-glururonidase having an exposed galactose residue and a pharmaceutically acceptable carrier such as Tris/HCl buffer..

Seemann in view of Mattes or Winkelhake do not explicitly teach that the pharmaceutical composition further comprises an agent that lowers the intracellular pH of tumor cells.

Bosslet teaches that that activity of β-glucuronidase increases at a pH that is lower than physiological pH (page 236, 2nd col.).

Jahde teaches methods of lowering intracellular pH of tumors comprising administering glucose (page 6210, 2nd column, *Results*).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the references so as to modify the pharmaceutical composition as taught by Seemann in view of Mattes or Winkelhake to include an agent that lowers the intracellular pH of a tumor in view of Bosslet and Jahde. One would have bee motivated to do so because Bosslet teaches that the activity of β-glucoronidase increases at a pH that is lower that physiological pH and Jahde provides agents which are capable of reducing intracellular pH. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifing the pharmaceutical composition as taught by Seemann in view of Mattes or Winkelhake to include an agent that lowers the intracellular pH of a tumor in view of Bosslet and Jahde, one would achieve a pharmaceutical composition having an agent which increases the enzymatic activity of β-glucuronidase.

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Seemann (Canadian Patent Application 2,062,047; cited in IDS;) in view of Mattes (U.S. Patent 4,859,449; issued 08/1989) or Winkelhake (Winkelhake, J. Biological Chemistry, 251(4): 1074-1080, 1976) and further in view of Bagshawe (U.S. Patent 5,632,990; issued 05/1997; filed 12/1990).

Seemann in view of Mattes or Winkelhake teach, as applied to claims 1-7, 9-13 and 15-16 above, a pharmaceutical composition comprising a recombinantly made fusion glycoprotein

comprising the antigen binding fragment of the monoclonal antibody BW431/26 linked to a β-glururonidase having an exposed galactose residue and a pharmaceutically acceptable carrier such as Tris/HCl buffer.

Seemann in view of Mattes or Winkelhake do not explicitly teach that the pharmaceutical composition further comprises galactose.

Bagshawe teaches the use of galactosylated antibody constructs for the purpose of increased clearance and further teaches methods that comprise the additional use of a substance for blocking glactose residues for the purpose of maintaining a high level of conjugate in the plasma until the galactose receptors are again free to take up the galactosylated conjugate. Bagshawe teaches that asialofetuin binds strongly to galactose receptors but that less immunogenic substances may be identified col. 4, lines 33-41).

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the references so as to modify the pharmaceutical composition as taught by Seemann in view of Mattes or Winkelhake to include galactose for the purpose of temporarily decreasing clearance of the fusion glycoproteins or conjugates in view of the teachings of Bagshawe et al.. One would have been motivated to do so because Bagshawe et al. teach the addition of a second substance to block galactose receptors from binding with the galactosylated conjugate. Thus, one of ordinary skill in the art would have had a reasonable expectation of success in using galactose as a substance for temporarily decreasing clearance of the fusion glycoproteins or conjugates because the receptors are galactose receptors.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 6-7, 9, 12 and 15-16 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6, 9-11 and 15-16 of U.S. Patent No. 7,060,495. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compound comprising two or more antigen binding regions which binds to a tumor-associated antigen such as CEA linked to at least one prodrug activating enzyme such as b-glucuronidase and a glycosylated component such as galactose or mannose claimed in the conflicting patent appears to fall within the same scope of a compound comprising a bifunctional fusion glycoprotein or bifunctional glycoprotein conjugate an exposed terminal carbohydrate complememtn such as galactose or mannose and at least one portion which possess enzymatic activity and a second portion which specifically binds to an epitope of a tumor-specific antigen claimed in the application under examination.

Therefore, NO claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Patent Examiner
Art Unit 1642

BF